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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,961	MOCK, MICHELE	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-11 and 16-36* is/are pending in the application.

4a) Of the above claim(s) *8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted on 8/10/04 is made. Claims 16-36 are currently under examination. Claims 8-11 are withdrawn from consideration because they are directed to non-elected claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 16-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16, 22, 27 and 32 are vague and indefinite because it recites "mutant strains of *B.anthracis* carrying one or more mutations selected from mutations in at least one gene encoding a protein responsible for a toxic effect selected from the group consisting of a lethal factor and an endematogenic factor, in *B.anthracis,* ..."; however, the claims fail to recite what the mutation does, e.g., can the strain still produce a toxin, do the mutations render the exotoxins non-toxic, etc.? If there is a mutation in lethal factor, can the strain still produce endematogenic factor? Additionally, it is unclear what is encompassed by "one or more mutations". Where are these mutations and how many mutations are included in this scope? It is unclear what strains would fall under this description and the specification does not further clarify. Additionally, while the

specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. The phrase " , in *B.anthracis,"* also seems unnecessary in the claims and only serves to confuse the claim. The claims should positively state that the mutation results in a gene incapable of producing the toxin or renders the toxin inactive. Appropriate correction is required.

Claims 16, 22, 27 and 32 are also vague and indefinite due to the phrase "combined *at least with* a pharmaceutically acceptable carrier". The phrase "at least with" confuses the claims. The claims uses open language and therefore allow for ingredients other than a pharmaceutically acceptable carrier. Accordingly, this phrase is unnecessary and only serves to confuse the claims.

Claims 18, 22, 28 and 33 recite "comprises at least one detoxified exotoxin selected from the group consisting of a lethal factor and an edematogenic factor, which have been detoxified". This language is redundant. The claim recites that the exotoxins are detoxified so it is unnecessary and confusing to again recite the phrase "which have been detoxified". Correction is required.

Claims 19, 21, 24, 26, 29, 31, 34 and 36 are vague and confusing because of the use of brackets within the parentheses, e.g., "(Collection Nationale de Cultures et de Microorganismes [National Collection of Cultures and of Microorganisms] held by the

Institut Pasteur under the number 1-2271, dated July 28, 1999)". Brackets generally indicate material which is to be deleted from the claim. It is unclear whether this information is intended to be printed. The use of commas in lieu of brackets is suggested.

Claims 20, 25, 30 and 35 recite the limitations "***the*** purified protective antigens derived from any wild-type or mutated Sterne strain of *B.anthracis*" and "***the*** recombinant produced protective antigens of *B.anthracis*" . There is insufficient antecedent basis for this limitation in the claims. The wording should be changed to "a purified protective antigen isolated from any wild-type or mutated Sterne strain of *B.anthracis* and a recombinantly produced protective antigen of *B.anthracis".*

Claim Rejections - 35 USC § 112-Deposit Requirement

3. Claims 19, 21, 24, 26, 29, 34, and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. See rejection under "112-first paragraph Deposit- in the previous Office Action.

Applicant's Representative has stated that Applicants have confirmed that the materials have been deposited under the Budapest Treaty and that is has been accepted by an International Depository Authority under the Treaty, etc.. However, this is insufficient to satisfy the requirement.

If the deposit has been made under the provisions of the Budapest Treaty, there must be either a filing of an affidavit or declaration by applicant or assignees or a

statement by an attorney of record who has authority and control over the conditions of the deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be replaced if viable samples cannot be dispensed by the depository is required. Neither of these conditions was met. The attorney of record's statement is not "a statement by an attorney of record who has authority and control over the conditions of the deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be replaced if viable samples cannot be dispensed by the depository is required", but is merely a statement stating that Applicants are in control. Correction is required, e.g., either an affidavit or declaration by applicant or assignees or a proper statement by the attorney of record over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be replaced if viable samples cannot be dispensed by the depository is required.

Claim Rejections - 35 USC § 112-Enablement

4. Claims 16-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enables 'vaccines and immunogenic compositions which comprise an isolated protective antigen from B.anthracis and killed spores from a non-encapsulated, toxigenic *B.anthracis* strain, i.e., a strain which carries

the pX01 plasmid and lacks the pX02 plasmids (also spores from Sterne strain 7702 which has these properties' and, does not reasonably provide enablement for "An acellular immunogenic composition/vaccine capable of inducing an immune response against B.anthracis infections, comprising: an isolated protective antigen (PA) from B.anthracis, and killed and purified spores obtained either from mutant strains of B.anthracis carrying one or more mutations selected from mutations in at least one gene encoding a protein responsible for a toxic effect selected from the group consisting of a lethal factor (LF) and an endematogenic factor (EF), in B.anthracis, or from mutant strains of B.anthracis lacking pXO2 plasmids, combined at least with a pharmaceutically acceptable vehicle". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are drawn to "acellular immunogenic compositions or vaccines capable of inducing an immune response against *B.anthracis* infections, characterized in that it comprises: a protective antigen (PA), killed spores obtained either from mutant strains of *B. anthracis* carrying one or more mutations chosen from mutations in at least one gene encoding a protein responsible for a toxic effect selected from the group consisting of lethal factor and endematogenic factor, in *B. anthracis*, or from mutant strains of *B. anthracis* lacking pXO2 plasmids, combined at least with a pharmaceutically acceptable vehicle'. Dependent claims recite that the spores may be derived from the Sterne 7702 strain, the RPLC strain and the RP42 strain. However, the instant specification only provides immunization results from experimentations

carried out using protective antigen and killed spores derived from the Sterne 7702 strain. The Sterne 7702 strain carries only the plasmid pX01 which carries genes which encode the protective antigen (PA), lethal factor (LF) and the edematogenic factor (EF) and does not carry the pXO2 plasmid which carries the genes which synthesize the capsule. Accordingly, the Sterne 7702 strain is a toxigenic, non-encapsulated strain. The instant claims read on a much broader scope than what has been demonstrated to be effective in the instant specification. More specifically, they read on vaccines and compositions which comprise killed spores derived from strains which do not carry the pX01 plasmid, strains which do not carry either the pX01 and pX02 plasmid and mutant strains which carry mutated genes for either LF or EF. These strains are very different from the Sterne 7702 strain and the prior art has shown that they have a great deal of variation in the their immunogenic and protective effects. The instant claims even allow for an active toxin to still be present, as a mutant strain with a mutation just in one of the toxins is encompassed by the instant claims. Pezard et al. (Infect. Immun. Apr.1995, 63(4): 1369-1372) teaches that animals immunized with strains which were deficient in the production of PA did not produce a good antibody response to EF or LF. In contrast, when LF or EF was produced by strains which also produce PA, a significant increase in the response against LF or EF was observed. The article by Pezard shows there is great variability in the immune response and the ability to protect against infection in various mutant strains, see Tables 1 and 2 on page 1371. Ivins et al. (Eur. J. Epidemiology. Mar. 1988. 4(1): 12-19) teaches that immunization with mutant strains carrying only the pX02 plasmid and not the pX01 plasmid (i.e., non-toxigenic,

encapsulated strains) did not provide any protection, nor did double mutants which contained neither the pX01 or pX02 plasmids. Ivins teaches that strains which did not produce any toxin components were not protective. Ivins et al (Infect. Immun. May 1986, 52(2):454-8) teaches that immunization with two non-toxigenic, encapsulated ($pX01^-$, $pX02^+$), Pasteur strains neither provided protection nor elicited titers to any of the toxin components. Ivins teaches that to immunize successfully against anthrax toxin or spore challenge, the strains of *B.anthracis* must produce the toxin components specified by the pX01 plasmid. The prior art has established that immunogenicity of *B.anthracis* mutant strains varies greatly. The spores derived from these strains would therefore vary in the same manner. The specification also fails to teach where and what mutations would detoxify the lethal factor or endematogenic factor. The scope of the current claims read on spores obtained from a strain which carries the genes for capsule making and can still produce a functional toxin, e.g, only a mutation in one of the toxins is recited. These would appear to be toxic immunogens. As stated above, the *B.anthracis* vaccine art is highly unpredictable. Without specific guidance and demonstration, the broad scope of the invention is not enabled.

Accordingly, the specification only enables vaccines and immunogenic compositions which utilize killed spores from a non-encapsulated, toxigenic *B.anthracis* strain, i.e., a strain which carries the pX01 plasmid and lacks the pX02 plasmids, e.g., from the Sterne strain.

Response to Applicants' Arguments:

Applicants argue that Pezard et al has taught that pXO1 may be important in the survival of *B.anthracis* in a host. They argue that mutants producing EF, LF or EF and LF elicited a weak and low specific antibody response. They argue that there is no link between the properties of the killed spores and results relating to living spores. These arguments have been fully and carefully reviewed but are not deemed persuasive. The instant claims do not require pXO1, nor do they require strains lacking pXO2. Killed spores which come from strains that can produce either a functional LF or EF and contain a pXO2 plasmid (can make a capsule) are included; e.g., mutant strains carrying a mutation in at least one gene encoding a protein selected from the group consisting of lethal factor or endomatogenic factor. These strains would be lethal. The scope of the claims is not commensurate in scope with what is taught in the specification. Only results and methods using utilize killed spores from a non-encapsulated, toxigenic *B.anthracis* strain, i.e., a strain which carries the pX01 plasmid and lacks the pX02 plasmids, e.g., from the Sterne strain are shown. The scope of invention should be limited accordingly.

Claim Rejections - 35 USC § 103

5. Claims 16, 17, 19, 20-22, 24-27, 29-32, and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Kraevets et al. Microbiology Res. Inst. July 1998, Derwent abstract only).

Kraevets et al teach a mixed anthrax vaccine comprising living spores of a non-encapsulated strain of *B.anthracis* and a protective antigen of *B.anthracis*. *B.anthracis* is normally encapsulated. It is well known in the art that the pX02 plasmid is

responsible for capsule production. Accordingly, the strain used to obtain the live spores in the Kraevets reference is encompassed by the language of the instant claims. Although the reference does not specifically recite that the spores came from one of the specific strains recited in instant claims 19, 21, 24, 26, 29, 31, 34 and 36, it was well known in the prior art at the time the invention was made that the Sterne 7702 strain is a nonencapsulated strain which carries only the pXO1 plasmid and not the pXO2 plasmid. Additionally, a strain without a capsule would be considered to be a mutant 'lacking a gene encoding a protein responsible for a toxic effect'. Use of the specific strains recited in the dependent claims does not appear to be a critical factor as long as the strain meets the criteria set forth in the independent claims. A different strain with the same properties would have been an obvious functional equivalent.

However, Kravets does not disclose that the spores to be used in the vaccine can be killed. It was well known in the prior art at the time the invention was made that live spores from *B.anthracis* had high lethality and were a risk to work with in the laboratory. Live spore vaccines were only approved for veterinary use and not human use. Killed anthrax vaccines were well known in the prior art to be safe and efficacious when used in humans. Absent a showing of new or unobvious results, it would have been obvious to substitute killed spores of a non-encapsulated strain of *B.anthracis* in place of the live spores taught by Kraevts because doing so would allow for easier manipulation in the laboratory and a reduced incidence of lethality in the host to be vaccinated.

Response to Applicants Arguments:

Applicants argue that it would not have been obvious to use killed spores because killed microorganisms are used only when attenuation is difficult to obtain and they generally provide less effective protection. They argue that since attenuation of *B.anthracis* was well-known, the use of killed spores would not have been obvious. This has been fully and carefully considered, but is not deemed persuasive. It has long been known in the prior art that live spores from *B.anthracis* have high lethality and are a risk to work with in the laboratory. Live spore vaccines are only approved for veterinary use and not human use. Killed anthrax vaccines were well known in the prior art to be safe and efficacious when used in humans. Substituting killed spores of a non-encapsulated strain of *B.anthracis* in place of the live spores taught by Kraevts would have been obvious to one of ordinary skill in the art at the time the invention was made because it would allow for easier manipulation in the laboratory and a reduced incidence of lethality in the host to be vaccinated.

6. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

J Graser 10/27/04

Jennifer Graser
Primary Examiner
Art Unit 1645